CHAPTER 24

Bone sarcomas

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Bone sarcomas are extremely rare neoplasms, which precludes determination of their true incidence. Approximately 2,570 new cases are identified annually in the United States. Population-based tumor registries seldom separate bone sarcomas into various histologic types.

Osteosarcoma is the most common malignant primary bone tumor (excluding multiple myeloma), comprising 30% of all such malignancies. The annual incidence of osteosarcoma is approximately 800 cases per year in the United States. Chondrosarcoma is the second most common malignant primary tumor of bone; its annual incidence is approximately half that of osteosarcoma. Ewing's sarcoma represents approximately 6% of all primary malignant bone tumors, with an annual incidence of 200 cases. Malignant fibrous histiocytoma (MFH) comprises < 1% of primary bone sarcomas.

Epidemiology

Gender The incidence of primary bone sarcomas is higher in males than in females regardless of histologic type. A low-grade variant of osteosarcoma (parosteal osteosarcoma) is observed more frequently in females.

Age Osteosarcoma and Ewing's sarcoma develop primarily in children and adolescents. A biphasic pattern of incidence of osteosarcoma has been observed that peaks in adolescents (rapid growth of long bones) and in the elderly (secondary tumors arising in association with Paget's disease or within previously irradiated tissue). Chondrosarcomas are rarely seen in skeletally immature patients. They usually develop in middle-aged and older adults. MFH is observed in adults.

Race No predilection has been noted in any particular race. However, Ewing's sarcoma is extremely rare in American and African blacks.

Disease site Any bone and any site within a given bone may be affected. Most osteosarcomas occur in the metaphyseal region of skeletally immature long bones (ie, distal femur, proximal tibia, and proximal humerus), which have the greatest growth potential. Ewing's sarcoma is classically described as a diaphyseal lesion but may arise in any region within an involved long bone. It commonly arises in the flat bones of the pelvis and scapula. Primary bone tumors of any histologic type are extremely rare in the spine and sacrum.

Survival Low-grade sarcomas are associated with the most favorable survival, which approaches 90% in patients with adequately treated tumors. With regard

to high-grade sarcomas, survival has improved dramatically in patients with osteosarcoma or Ewing's sarcoma due to the advent of effective multiagent chemotherapy regimens. Survival has improved from historic rates of < 20% to current rates of 50%-75% with multimodality therapy.

Etiology and risk factors

For the majority of bone sarcomas, no specific etiology has been established. A few predisposing factors have been identified.

Genetic factors Children with familial retinoblastoma have a 13q chromosome deletion and an increased incidence of osteosarcoma.

Radiation therapy Bone sarcomas constitute a rare but devastating consequence of therapeutic irradiation. Radiation-associated sarcomas develop within the radiation field, usually after a latent period of at least 3 years. The majority of these tumors are osteosarcomas. MFH and other histologies also can arise within a radiation field.

Chemotherapy Alkylating agents and anthracyclines administered for unrelated cancers have been implicated as etiologic factors in the development of second malignant neoplasms, particularly osteosarcoma.

Preexisting benign tumors/conditions Osteosarcomas can arise in association with Paget's disease and rarely in association with benign bone tumors (ie, fibrous dysplasia). Chondrosarcomas can develop in the cartilaginous component of osteochondromas (solitary and multiple hereditary exostosis) and in patients with enchondromatosis (Ollier's disease and Maffucci's syndrome). MFH can arise in association with bone infarcts.

Trauma A traumatic event often prompts medical intervention, at which time the bone sarcoma is detected. The short temporal relationship between the traumatic event and the diagnosis of the tumor usually rules out a causal relationship.

Orthopedic implants Case reports of bone sarcomas arising in the region in which a metallic prosthetic device has been implanted have been published. The rarity of these clinical situations relative to the vast number of devices implanted makes a causal relationship unlikely.

Signs and symptoms

Local symptoms Localized pain and swelling are the hallmark clinical features of bone sarcomas. The pain, which initially is insidious and transient, becomes progressively more severe and unremitting. Localized soft-tissue swelling, with or without associated warmth and erythema, may be present. A joint effusion may be observed, and range of motion of the adjacent joint may be limited and painful. Movement or weight-bearing of the involved extremity may exacerbate local symptoms.

Patients with tumors arising in the lower extremities can present with a painful limp. The neurovascular examination of the affected extremity is usually normal. Regional lymph nodes are rarely involved.

Pathologic fracture may also be a presenting sign, although a history of pain prior to fracture usually can be elicited.

Constitutional symptoms are rare in patients with bone sarcoma, but such symptoms as fever, malaise, and weight loss can be observed in those with Ewing's sarcoma.

Screening and diagnosis

Currently, there is no screening test for primary bone sarcomas. The diagnosis must be made by clinical and radiographic evaluations and confirmed by histopathologic analysis of biopsy-obtained tissue.

Physical examination should include an assessment of the local extent of the soft-tissue mass, if present, and its relationship to the adjacent joint.

Laboratory studies A CBC may demonstrate anemia and/or a leukocytosis associated with Ewing's sarcoma, but, in general, results of these studies fall within the normal range. Alkaline phosphatase and lactic dehydrogenase (LDH) levels may be elevated in patients with osteosarcoma or Ewing's sarcoma. An abnormal glucose tolerance test may be observed in patients with chondrosarcomas.

X-rays Biplanar (AP and lateral) plain radiographs of the affected extremity provide critical information on the nature of the bone lesion. The specific site of involvement within the bone, pattern and extent of bone destruction, type of periosteal changes, presence of matrix mineralization within the tumor, and presence of soft-tissue extension may be gleaned from plain films.

CT Standard CT scans provide further delineation of many of these changes.

MRI is the imaging study of choice for the evaluation of the extent of an associated soft-tissue mass and the relationship of the tumor to the neurovascular structures, surrounding soft tissues, and the adjacent joint. The intramedullary extent of the tumor and presence of skip metastases within the bone are best demonstrated by MRI.

Bone scan A bone scan is performed to screen for distant osseous metastases.

Chest radiographic studies A plain film of the chest is required in any patient suspected of having a bone sarcoma. Once the diagnosis of malignancy has been established, a CT scan of the chest is a critical part of initial staging.

Biopsy With few exceptions, a biopsy must be obtained to confirm the diagnosis. Tissue may be obtained by percutaneous (closed) or surgical (open) techniques. The biopsy should be performed by personnel expert in percutaneous biopsy techniques who are familiar with bone tumors and their treatment.

Biopsies performed at referring institutions have been reported to be associated with a higher incidence of misdiagnosis and complications, which may affect patient outcome. Optimally, the biopsy should be performed at the institution where definitive treatment will be given.

TABLE 1: Surgical staging of bone sarcomas

Stage	Grade	Site
IA	Low	Intracompartmental
IB	Low	Extracompartmental
IIA	High	Intracompartmental
IIB	High	Extracompartmental
III	Any regional or distant metastasis	Any

From Enneking WF, Spanier SS, Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 153:106–120, 1980.

Pathology

Histologic subtypes Current histopathologic classification of bone neoplasms is based on the putative cell of origin. Malignant tumors may arise from any cellular constituent present in bone, including osteogenic (osteosarcoma), chondrogenic (chondrosarcoma), hematopoietic (multiple myeloma, lymphoma), vascular (angiosarcoma, hemangioendothelioma, leiomyosarcoma), lipogenic (liposarcoma), neurogenic (neurofibrosarcoma, chordoma), and histiocytic and fibrohistiocytic (MFH, Ewing's sarcoma) elements. Histologic subtyping is based on the predominant cellular pattern present within the tumor, degree of anaplasia, and relationship of the tumor to the bone (intramedullary vs surface).

A monoclonal antibody (CD99) has been developed that recognizes a cell-surface glycoprotein (p30/32MIC2) in human Ewing's sarcoma and peripheral neuroectodermal tumor (PNET). There is strong immunoreactivity of CD99 in Ewing's sarcoma and PNET that aids in distinguishing these tumors from other small round-cell tumors of childhood and adolescence. Additional experience with CD99, however, demonstrates that it is not exclusively specific for Ewing's sarcoma and PNET.

Dedifferentiation Primary bone sarcomas can exhibit the phenomenon of "dedifferentiation." These neoplasms demonstrate a dimorphic histologic pattern, which is characterized by the presence of a borderline malignant or low-grade malignant tumor juxtaposed against a high-grade, histologically different sarcoma. Enchondromas, low-grade chondrosarcomas, low-grade variants of osteosarcoma (surface and intramedullary), and chordomas may all develop an area of high-grade spindle-cell tumor, usually MFH.

Metastatic spread Approximately 10%-20% of patients with osteosarcoma and 15%-35% of patients with Ewing's sarcoma have evidence of metastatic disease at initial presentation. In approximately 90% of patients with bone sarcomas, the initial site of distant metastasis is the lungs. Distant osseous sites, bone marrow, and viscera may also be involved as a manifestation of advanced disease, but involvement of these sites is less common and usually occurs after the development of pulmonary metastases. Regional lymph node involvement is rare.

Staging and prognosis

Staging system The staging system of the Musculoskeletal Tumor Society (MTS) is used currently (Table 1). This system is based on tumor grade (I = low or II = high), tumor extent (A = intraosseous involvement only or B = extraosseous extension), and presence of distant metastases, regardless of the extent of local disease (III). Patients with localized tumor may have stage IA, IB, IIA, or IIB disease.

Prognostic factors Many studies have demonstrated that tumor response to preoperative chemotherapy, as determined by histologic analysis of the resected specimen, is the most powerful predictor of survival for patients with osteosarcoma. Adverse prognostic indicators, such as an axial primary or elevated LDH and alkaline phosphatase levels, signal an even worse outcome.

Tumor size (low volume) and anatomic site (peripheral), absence of metastases at initial presentation, and good histologic response to chemotherapy are prognostic variables associated with better outcome in patients with osteosarcomas and Ewing's sarcoma. The translocation t(11;22), which results in the type 1 EWS-FLI1 fusion, is also a significant positive predictor of overall survival in Ewing's sarcoma.

For low-grade malignant tumors, adequacy of surgery is the most significant predictor of outcome.

Treatment

PRIMARY TREATMENT OF BONE SARCOMAS

Surgical excision is the mainstay of treatment for patients with low-grade sarcomas. For high-grade tumors, multimodality therapy is indicated. For most high-grade bone sarcomas, excluding chondrosarcoma, preoperative multiagent chemotherapy (three to four cycles) is followed by surgical extirpation of the primary tumor. Chemotherapy is reinitiated postoperatively after wound healing has occurred (usually 2-3 weeks after surgery).

For patients with Ewing's sarcoma, the optimal therapy for local tumor control is less well defined. Historically, radiotherapy has been a mainstay of local treatment. However, there has been a recent trend toward surgery, with or without radiotherapy, to achieve local tumor control. No prospective, randomized studies have been performed to define the relative role of each of these treatment modalities, but several retrospective studies suggest improvements in local tumor control and patient survival when surgery is satisfactorily performed. Patients with unresectable tumors or microscopic or macroscopic residual disease following tumor excision clearly require adjuvant radiotherapy to consolidate their local treatment.

Surgical treatment strategy

The MTS recognizes wide excision, either by amputation or a limb-salvage procedure, as the recommended surgical approach for high-grade sarcomas. A

wide excision removes the primary tumor en bloc along with its reactive zone and a cuff of normal tissue in all planes. Conceptually, this strategy is applicable to all high-grade sarcomas. Wide excision successfully controls local disease in ≥ 90% of patients.

The timing of surgery must be coordinated with the patient's chemotherapy schedule and with bone marrow recovery to minimize the period of systemic therapy. Generally, surgical intervention is postponed until the patient's absolute neutrophil count (ANC) has recovered to a level of ≥ 1,500/μL and platelet count, to a level of ≥ 70,000/μL.

Limb-salvage procedures

Wide tumor excision with limb preservation has supplanted amputation as the principal surgical method for eradicating local disease in patients with primary sarcomas of bone, regardless of histology or grade. Local tumor control and patient survival have not been compromised by this more conservative operative strategy. Refinements in surgical techniques and advances in bioengineering have increased the number of patients eligible for limb-salvage surgery. Currently, 75%-80% of patients may be treated with conservative surgery.

Successful limb-salvage surgery of the patient with a high-grade bone sarcoma is predicated on complete extirpation of the tumor, effective skeletal reconstruction, and adequate soft-tissue coverage. Planning for the operative procedure must begin far in advance to permit adequate time to procure the implant for reconstruction.

Types of resection Limb-sparing tumor resection falls into one of three types based on the anatomic site and extent of involved bone to be excised. Resection can involve (1) tumor-bearing bone and adjacent joint (osteoarticular), (2) tumor-bearing bone only (intercalary), or (3) whole bone and adjacent joints (whole bone).

Since most bone sarcomas arise in the metaphysis of the long bone near the joint, the majority of procedures performed for these tumors involve resection of both the segment of tumor-bearing bone and the adjacent joint (osteoarticular resection). Most of these resections are performed through the adjacent joint (intra-articular). When the tumor extends along the joint capsule or ligamentous structures and/or invades the joint, the entire joint should be resected (extra-articular) to avoid violating areas that have tumor involvement.

Reconstruction Prosthetic arthroplasty is the most common method by which the skeletal defect and adjacent joint are reconstructed. Osteoarticular allografts, intercalary allografts, and vascularized and nonvascularized autografts are also used, depending on the extent of resection and requirements for successful reconstruction.

Tumors in the immature skeleton

Tumors arising in the immature skeleton pose a unique problem for the orthopedic oncologist, particularly in patients with substantial projected growth of the involved extremity. The surgical management of bone sarcomas in very

young patients, with few exceptions, has entailed amputation or rotationplasty.

Custom-manufactured expandable metallic joint prostheses can be implanted to allow for skeletal growth in those children deemed candidates for limb-salvage surgery. The long-term outcome of this technique has been promising. However, multiple operative procedures should be anticipated to maintain a functional extremity.

Soft-tissue coverage

Adequate soft-tissue coverage is critical to the success of any limb-salvage procedure. Local transposition muscle flaps and free tissue transfers are extremely useful for providing a healthy, well-vascularized soft-tissue envelope to cover the reconstruction and reduce the risk of deep infection.

SURGICAL TREATMENT OF METASTATIC DISEASE

The most common site of metastatic involvement for bone sarcoma is the lungs. Patients who present with pulmonary metastases (10%-20% of patients with osteosarcoma) have a poor prognosis (5-year survival rate < 15%). Approximately 30%-40% of patients who present with localized disease and who subsequently develop resectable pulmonary metastases can undergo salvage treatment with reinduction chemotherapy and metastasectomy (see section on "Treatment of advanced osteosarcoma"). Patients with extrapulmonary metastases or unresectable pulmonary metastases have a uniformly poor prognosis. The objective of any surgical intervention in these patients, therefore, would be palliative.

CHEMOTHERAPY FOR OSTEOSARCOMA

The probability of 5-year disease-free survival for patients with osteosarcoma of the extremities treated with either amputation or limb-salvage surgery alone is < 20%. Although the incidence of local recurrence is low, microscopic dissemination is likely to be present in 80% of patients at the time of diagnosis, leading to distant metastases, mostly in the lungs and bones, within the first 6-12 months. The incorporation of chemotherapy as part of the standard therapeutic plan for osteosarcoma (Table 2) has improved both relapse-free and overall survival.

Neoadjuvant/adjuvant chemotherapy

To achieve better systemic control and decrease the degree of functional defect following surgery, neoadjuvant (presurgical) treatment programs have been developed by several centers. Early trials incorporated high doses of methotrexate, given weekly for 4 weeks with leucovorin rescue, prior to surgery. Subsequent modifications included the incorporation of bleomycin, dactinomycin (Cosmegen), and cyclophosphamide (Cytoxan, Neosar) into the regimen, with the further addition of doxorubicin.

The next generation of trials adjusted the adjuvant (postoperative) chemotherapeutic regimen, depending on the degree of tumor necrosis found at the time of surgery. Patients who had a good tumor response (> 90% necrosis) were

TABLE 2: Chemotherapy regimens for bone sarcomas

Drug/combination	Dose and schedule
T-12 regimens	
Preresection:	
Methotrexate	8-12 g/m^2 IV on day 1 of week 0, day 8 of week 1, day 29 of week 4, and day 36 of week 5
Leucovorin	10-15 mg PO every 6 hours for 10 doses beginning 20 hours after each methotrexate dose and completed when the serum methotrexate level is < 100 nmol/L. Additional leucovorin should be administered if elevated serum methotrexate levels are noted or if renal toxicity is present
BCD regimen	
Bleomycin	15 U/m^2 IV bolus × 2 (on days 15 and 16 of week 2)
Cyclophosphamide	600 mg/m^2/d IV bolus × 2 days (on days 15 and 16 of week 2)
Dactinomycin	600 µg/m^2/d IV bolus × 2 days (on days 15 and 16 of week 2)
Preoperative chemotherapy is completed in 6 weeks and followed by definitive surgery between day 43 of week 6 and day 50 of week 7	
Postresection regimen for patients with primary tumor grades 1 and 2 (less necrosis):	
Doxorubicin	25 mg/m^2 IV continuous infusion over 3 days (on days 57, 58, 59 of week 8; days 106, 107, 108 of week 15; days 155, 156, 157 of week 22; days 190, 191, 192 of week 27; and days 225, 226, 227 of week 32)
Cisplatin	120 mg/m^2 IV on day 57 of week 8, day 106 of week 15, day 155 of week 22 , day 190 of week 27, and day 225 of week 32
Methotrexate	As above on day 78 of week 11, day 99 of week 14, day 127 of week 18, and day 148 of week 21
BCD	Regimen as above on day 85 of week 12, day 134 of week 19, day 176 of week 25, and day 211 of week 30
Postresection regimen for patients with primary tumor grades 3 or 4 (more necrosis):	
Doxorubicin	As above on days 57, 58, 59 of week 8; days 106, 107, 108 of week 15; days 155, 156, 157 of week 22; and days 204, 205, 206 of week 29
Methotrexate	As above on day 78 of week 11, day 99 of week 14, day 127 of week 18, day 148 of week 21, day 176 of week 25, day 197 of week 28, day 225 of week 32, and day 246 of week 35
BCD	Regimen as above on days 85 and 86 of week 12, days 134 and 135 of week 19, days 183 and 184 of week 26, and days 232 and 233 of week 33

NOTE: Administering this protocol safely and successfully requires extensive experience and excellent supportive care.

Meyers PA, Gorlick R, Heller G, et al: J Clin Oncol 16:2452–2458, 1998.

Table prepared by Ishmael Jaiyesimi, DO

treated with additional cycles of the neoadjuvant regimen; those who had a poor response received cisplatin and doxorubicin. It remains controversial whether altering the adjuvant chemotherapeutic regimen for patients with poor histologic response truly changes their event-free survival.

The addition of ifosfamide (Ifex) did not improve survival in pediatric osteosarcoma patients in a recent study. A Children's Oncology Group (COG) study reported no difference in outcome between a three-drug combination of cisplatin, doxorubicin, and high-dose methotrexate and a four-drug regimen of the same drugs plus ifosfamide. The European Osteosarcoma Intergroup (EOI) reported no difference in histopathologic response to preoperative chemotherapy and overall survival in patients randomized to receive a two-drug regimen with doxorubicin and cisplatin or a complex multidrug protocol containing doxorubicin, cisplatin, and high-dose methotrexate among other agents.

The EOI also investigated standard-dose vs increased-dose intensity (dose-dense) cisplatin and doxorubicin for patients with operable osteosarcoma of the extremity. The overall dose intensity was increased by 24% for cisplatin and 25% for doxorubicin. Good histologic response (≤ 10% viable tumor) was significantly higher in the intensified arm (51% vs 36%). Unfortunately, overall survival at 4 years was not significantly different (61% for standard and 64% for intensified).

The actuarial 5-year event-free survival rate in patients presenting with localized, primarily extremity osteosarcoma is > 70%. Regardless of the multidrug therapy used, event-free survival correlates with histologic response. Patients with > 90% tumor necrosis have a > 80% probability of 5-year event-free survival. Complete responses are more likely to occur in patients with the nonchondroblastic subtype and in those whose peak serum methotrexate levels are > 700 μmol/L. Chemosensitivity also seems to be diminished in patients with metastatic disease at presentation.

Poor responders Patients with poor tumor response may represent 30%-60% of the population with extremity osteosarcoma. For these patients, more effective treatment regimens, such as dose intensification using growth factors and stem-cell support, and newer agents need to be evaluated.

Alternative approaches One alternative approach to neoadjuvant therapy is adjuvant therapy. A randomized study of the Pediatric Oncology Group (POG) demonstrated no detectable difference in event-free survival whether chemotherapy was offered before or after surgery. The feasibility of safely performing limb-salvage surgery in these patients, however, has not been studied directly. Additionally, intra-arterial delivery of cytotoxic agents has shown no specific survival benefit but provides increased concentration of chemotherapy to the primary tumor, which may impact favorably on the extent of the resection for patients undergoing limb-salvage surgery.

TREATMENT OF ADVANCED OSTEOSARCOMA

Axial primary tumor For the 10%-15% of patients who present with axial primary osteosarcoma, neoadjuvant chemotherapy should be considered to

reduce the tumor burden prior to surgery or radiation therapy. The Cooperative Osteosarcoma Study Group (COSS) reported that 11.4% of their patients treated before 1999 had proven metastases at diagnosis. Actuarial survival at 5 and 10 years was 29% and 24%, respectively, when treated with preoperative and postoperative multiagent chemotherapy as well as aggressive surgery for all resectable lesions. Multivariate Cox regression analysis demonstrated that multiple metastases at diagnosis and macroscopically incomplete surgical resection are significantly associated with inferior outcomes in patients with primary metastatic osteosarcoma.

The prognosis for patients who develop metachronous skeletal osteosarcoma (OS) has been considered grave compared with that for patients with relapse limited to the lungs. Investigators at Memorial Sloan-Kettering Cancer Center reported that in a small subset of patients who developed metachronous OS at 24 months or more from the initial diagnosis (11 of 23 patients with OS), combined-modality therapy with surgery and aggressive chemotherapy resulted in a 5-year postmetachronous survival rate of 83%, vs 40% for patients receiving monotherapy (usually surgery) only. These results refute an earlier pessimistic sentiment (*Aung L, Gorlick R, Healey JH, et al: J Clin Oncol 21:342-348, 2003*).

Pulmonary metastasis Patients with metastatic disease to the lungs should be evaluated for resection. Following aggressive pulmonary metastasectomy, < 25% of patients will achieve prolonged relapse-free survival. Hence, these patients may also benefit from aggressive "secondary" adjuvant chemotherapy.

Chemotherapy should also be considered for patients whose pulmonary metastases are unresectable, with the intention of performing surgery in those who have a sufficient response; approximately 10% of such patients may become long-term survivors.

Poor-risk patients or patients with recurrent disease are candidates for clinical trials that evaluate chemotherapy dose intensification or newer therapeutic agents. Alternatively, the POG demonstrated stabilization of disease in patients with recurrent or refractory osteosarcoma employing the combination of cyclophosphamide and topotecan (Hycamtin), although objective responses were rare. Interestingly, investigators at the Mayo Clinic reported significant palliation of pain in osteosarcoma patients with symptomatic bone metastases who were treated with samarium-153 ethylene diaminetetramethylene phosphonate (^{153}Sm-EDTMP), a bone-seeking radiopharmaceutical, in conjunction with stem-cell rescue. Nonhematologic side effects were minimal.

CHEMOTHERAPY FOR EWING'S SARCOMA

Prior to the availability of effective chemotherapeutic agents, < 10% of patients with Ewing's sarcoma survived beyond 5 years. The first intergroup Ewing's sarcoma study demonstrated an improved survival rate for patients receiving systemic therapy with the VACA regimen (vincristine, Actinomycin D [dactinomycin], cyclophosphamide, Adriamycin [doxorubicin]) for the first three drugs only and for patients receiving VAC plus bilateral pulmonary irradiation. In the future, selection of a specific therapeutic regimen may be influ-

enced by the presence of molecular markers in addition to standard clinical criteria.

In the second intergroup study, the addition of doxorubicin to VAC, when given on an intermittent schedule and at a higher dose, improved the 5-year relapse-free survival rate to 73%; this rate was almost double that of the cohort of patients not receiving doxorubicin as part of their treatment. The worst results were observed in patients with pelvic, proximal extremity, and lumbar vertebral lesions.

A phase III study investigating the addition of ifosfamide and etoposide to standard chemotherapy (doxorubicin, vincristine, cyclophosphamide, and dactinomycin) for patients with Ewing's sarcoma and PNET of the bone significantly improved overall survival for patients with localized disease (72% vs 61%), but it did not affect the outcome for patients with metastatic disease (overall survival 34% vs 35%). In addition to biologic adverse features at presentation (male sex, age, high LDH levels, anemia, fever, axial locations, non-type 1 fusion transcripts, and lack of feasibility of surgical resection), independent prognostic factors also include the type of chemotherapy and degree of tumor necrosis.

CHEMOTHERAPY FOR ADVANCED EWING'S SARCOMA

Aggressive combination chemotherapy and irradiation can lead to prolonged disease progression-free survival, even in patients with metastatic disease. The combination of ifosfamide (1.6 g/m^2) and etoposide (100 mg/m^2 given on days 1-5) results in high response rates of > 80%. Unfortunately, late recurrences are not uncommon.

Dose intensification of active chemotherapeutic compounds, including those employing autologous stem-cell rescue, has not been definitively shown to significantly improve survival of patients with poor-risk and metastatic Ewing's sarcoma and PNET. Newer therapeutic agents should be tested.

In patients with recurrent or refractory Ewing's sarcoma, the combination of cyclophosphamide and topotecan was shown to possess significant antitumor activity by the POG.

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